Chapter 14
Viruses, Cancer, and Immunology

SUMMARY

Section 14.1

- Viruses are simple genes, made up of RNA or DNA, that infect cells and take over their replication, transcription, and translation machinery.
- Viruses are characterized by their structure, their type of nucleic acid, whether it is single- or double-stranded, and their mode of infection.
- Viruses are known to cause many diseases, and they may be very specific to a particular species and cell type.
- Viruses enter the cell by binding to specific receptors on the cell. Once inside the cell, the virus may replicate, form new viruses, and burst the cell.
- The virus may also hide its DNA by incorporating it into the host's DNA.

Section 14.2

- Retroviruses have a genome based on RNA. When they infect a cell, their RNA is turned into DNA by reverse transcriptase. The DNA is then incorporated into the host's DNA genome as part of the replication cycle for the virus.
- Retroviruses all have certain genes in common, such as the genes for coat proteins, the gene for reverse transcriptase, and the one for envelope proteins.
- Some retroviruses also have identifiably unique genes, like the sarcoma oncogene in the Rous sarcoma virus.

Section 14.3

- Vertebrates have a complicated and elegant system of defense called the immune system.
- One type of immunity, called innate immunity, consists of physical barriers, such as skin, and cellular warriors, such as dendritic cells. This system is always present and waiting to attack invading organisms or even cancerous cells.
- Another type of immunity, called acquired immunity, is based on two types of T cells (killer T cells and helper T cells) and on B cells. These cells are generated randomly with receptors that can be specific for an unimaginable number of antigens.
- When these cells encounter their specific antigens, they are stimulated to multiply, exponentially increasing the number of cells that can fight the invading organism.
- Acquired immune cells also leave behind memory cells so that, if the same pathogen is seen again, the body is faster to eliminate it.
- Immune cells must also be able to recognize self from nonself. T cells and B cells are conditioned, in their early stages of development, not to recognize proteins from that individual.
- In some cases, this system breaks down, and a person may be attacked by his or her own immune system, which may lead to an autoimmune disease.

Section 14.4

- All potentially fatal cancers have several things in common, such as having cells that are immortal, that divide despite "stop growth" signals from nearby cells, that stimulate blood-vessel formation near to themselves, and that spread to other parts of the body.
- The development of cancer requires multiple breakdowns in normal metabolism.
- Most cancers have been linked to specific genes called oncogenes or to tumor-suppressor genes. When these genes are mutated, the cell loses the ability to control its replication.
- There are many classical ways to fight cancer, such as radiation therapy and chemotherapy. Both of these are very hard on healthy cells and, therefore, on the patient.
- Novel techniques using viruses are now being tried to target cancer cells more directly, and some of these are showing tremendous promise.

Section 14.5

- Human immunodeficiency virus (HIV) is the most infamous of the retroviruses, as it is the causative agent of acquired immunodeficiency syndrome (AIDS). This disease affects more than 40 million people worldwide and has continually thwarted attempts to eradicate it
- HIV offers a classic example of the mode of operation of retroviruses. The HIV infection begins when the virus particle binds to receptors on the surface of a cell. The viral core is inserted into the cell and partially disintegrates. The reverse transcriptase catalyzes the production of DNA from the viral RNA. The viral DNA is integrated into the DNA of the host cell.
- HIV has several characteristics that lead to its persistence and eventual lethality. Ultimately, it is deadly because of its targets, the helper T cells.
- HIV is difficult to kill because it is difficult to find. For an immune system to fight a virus, it needs to locate specific macromolecules that can be bound to antibodies or T-cell receptors. The reverse transcriptase of HIV is very inaccurate in replication. The result is rapid mutation.
- Scientists are fighting AIDS on several fronts, including searching for a vaccine and using antiretroviral therapies.

LECTURE NOTES

This chapter begins with a general discussion of viruses and brings in some topics of current public interest. Many students will find this information of particular interest. One or, perhaps, two lectures may be spent on this material dependent upon the depth of presentation and specific interests of the students.

LECTURE OUTLINE

I. Viruses
   A. Importance of viruses
   B. Virus structure
   C. Families of viruses
   D. Virus life cycles

1. Lytic pathways
2. Lysogeny
3. SV40 as an example
4. Oncogenes

E. Viral attachment & infection

II. Retroviruses
- A. Reverse transcriptase
- B. HIV

III. The immune system
- A. Innate immunity
- B. Acquired immunity
  1. T-cell functions
  2. T-cell memory
- C. Molecular aspects
  1. Antibodies
  2. Self and non-self

IV. Cancer
- A. Hallmarks of cancer cells
- B. Causes of cancer
- C. Oncogenes
- D. Tumor suppressors
- E. Viruses and cancer
- F. Viruses as cancer cures

V. AIDS
- A. Virus characteristics
- B. HIV confounds the immune system
- C. Fighting AIDS
  1. Vaccines
  2. Antiviral therapy

ANSWERS TO PROBLEMS

14.1 Viruses

1. Some viruses have DNA and some have RNA. In some cases, a viral genome is single-stranded and in others it is double-stranded.

2.

(a) The virion is the entire virus particle.
(b) The capsid is the protein coat that surrounds the viral nucleic acid.
(c) The nucleocapsid is the combination of the nucleic acid and the capsid.
(d) A protein spike is a membrane-bound protein that is used to help the virus attach to its host.

3. The main factors determining the family of a virus is whether its genome is DNA or RNA and whether it has a membrane envelope. Whether the nucleic acid is single- or double-stranded and the method of incorporation of the virus are also considered.

4. The virus attaches to a specific protein on the host cell's membrane and injects its nucleic acid inside the cell.

5. In the lytic pathway, the viral nucleic acid is replicated in the host cell and packaged into new virus particles that lyse the host cell. In the lysogenic pathway, the viral DNA is incorporated into the host DNA.
6. There is no correlation. Some viruses, such as Ebola virus, are fast acting and very lethal; others, such as HIV, are slow and just as lethal. The influenza virus is fast-acting, but it is rarely lethal these days.
7. One good choice would be a drug that attacks one of the specific protein spikes on the virus. This may be an antibody that attacks it, or a drug that blocks its ability to attach to the host cell. Another choice would be a drug that inhibits a key viral enzyme, such as the reverse transcriptase of a retrovirus, or the enzymes involved in repackaging the viruses.
8. Viruses can often switch from one pathway to another, based on the condition of the host cells. If the host is healthy, there is sufficient material to allow the virus to replicate and to produce new virions. If the host cell is starved or unhealthy, there may be insufficient energy and material to do so. In this case, lysogeny allows the DNA to incorporate in the host cell, where it can wait until the cell's health improves.
9. One example would be someone who had helper T-cells lacking a CD4 receptor. The HIV virus must bind to the CD4 receptor as part of its attachment process.

14.2 Retroviruses

10. A retrovirus has an RNA genome that must pass through a stage in which it is reverse-transcribed to DNA, and this DNA must recombine with the host's DNA.
11. Reverse transcriptase.
12. The first is that retroviruses have been linked to cancer. The second is that human immunodeficiency virus (HIV) is a retrovirus. The third is that retroviruses can be used in gene therapy.
13. Gene therapy is the process of introducing a gene into the cells of an organism that was missing functional copies of the gene.
14. Ex vivo gene therapy, in which the cells are removed from the patient before being infected with the virus carrying the therapeutic gene, and in vivo gene therapy, in which the patient is directly infected with the virus carrying the gene.
15. The two most common are the Maloney murine leukemia virus (MMLV) and adenovirus. Both must be manipulated so that the critical genes for replication are removed and replaced with an expression cassette containing the therapeutic gene.
16. When retroviruses, such as MMLV, are used, there is the danger that the therapeutic gene will incorporate in a place that will disrupt another gene. In more cases than would be predicted by random chance, this seems to occur in a place that disrupts a tumor-suppressor gene, causing cancer. There is also the danger that the patient will have a strong reaction to the virus used to introduce the therapeutic gene. In at least one case, this has had fatal consequences.
17. The biggest consideration is where the therapeutic gene has to go. Some viruses are very specific to their target cells, so if the problem is in the lungs, then a virus that is good at attacking lung cells, such as adenovirus, is a good choice. In this case, in vivo delivery would be superior, because lung cells cannot be removed

from the body and then replaced. However, if the problem is in an immune cell, then bone marrow cells can be removed and transformed and later given back to the patient, making ex vivo delivery an option.

18. There are dangers inherent to all forms of gene therapy. People who have SCID have such compromised immune systems that they cannot lead normal lives, and few other remedies allow them to lead normal lives. That made SCID a prime candidate for experimental techniques. Diabetes can be controlled effectively by other techniques that are well established and not as risky.

14.3 The Immune System

19. AIDS is the most well-known problem of a malfunctioning immune system. SCID is also high on the list. All allergies are immune system problems, as are autoimmune diseases. Many forms of diabetes are caused by an autoimmune disease in which a person's pancreatic cells are attacked by the immune system.
20. Innate immunity refers to a variety of protective processes, including skin, mucus, and tears as a first line of defense, and dendritic cells, phagocytes, macrophages, and natural killer cells as a second line of defense. These are always present, and the innate-immunity cells are always circulating in the body. Acquired immunity refers to the processes involving B cells and T cells, in which specific sets of them are activated in response to an antigen challenge, and these subsets then multiply.
21. One part includes physical barriers, such as skin, mucus, and tears. The cells of the innate immune system are dendritic cells, macrophages, and natural killer (NK) cells.
22. B cells, which make antibodies, killer T cells, which attack infected cells, and helper T cells, which help activate B cells.
23. MHCs are receptors on antigen-presenting cells. They bind to fragments of antigens that have been degraded by the infected cell and display it on their surface. T cells then bind to the infected cells.
24. Clonal selection refers to the process in which a particular T cell or B cell is stimulated to divide. Only the one bearing the correct receptor for the antigens being presented is selected.
25. The cells of the innate system initially attack a pathogen, such as a virus, bacteria, or even a cancerous cell. They then present antigens from the pathogen on their surfaces via their MHC proteins. The acquired immunity cells then recognize the MHC/antigen complex, bind to it, and begin the involvement of the acquired immunity system.
26. Interferon is a cytokine produced in very small quantities that stimulates natural killer cells, which attack cancerous cells. One of the first treatments for cancer was to give the patient interferon to stimulate NK cells. Having a large supply of cloned interferon is helpful, therefore, in fighting cancer.
27. When T cells and B cells are developing, they are, in a sense, "trained." If they contain receptors that recognize self-antigens, they are eliminated when they are still young. If they don't ever see any antigens they recognize, then they die by neglect. This leaves a set of precursors to T cells and B cells with receptors that recognize foreign antigens but not self-antigens.

28. Macrophages, part of the innate immune system, are the “double-edged sword.” Their presence is important to attack cancer cells, and if they do a thorough job, then the cancer cells are all destroyed. However, they also cause inflammation, which has recently been shown to indirectly lead to the progression of the cancer cells that survive.
29. The small noncoding RNA (ncRNA) of the herpes virus has been linked with its ability to evade the immune system.
30. The herpes virus produces a ncRNA that stabilizes the respiratory chain of the mitochondria of the host cell. This prevents the early destruction of the infected cell by the host’s immune system. At the same time, a micro RNA (miRNA) produced by the virus inhibits production of a protein on the surface of the cell that would otherwise attract NK cells.

14.4 Cancer

31. Cancer cells continue to grow and divide in situations in which normal cells do not, such as when they are not receiving growth signals from surrounding cells. They also continue to grow even if surrounding tissues are sending out “stop growth” signals. Cancer cells can co-opt the body’s vascular system, causing the growth of new blood vessels to supply the cancerous cells with nutrients. Cancer cells are essentially immortal. They can continue to grow and to divide indefinitely. Cancer cells can break loose, travel to other parts of the body, and create new cancerous areas, a process known as metastasis.
32. A tumor suppressor is a molecule that restricts the ability of a cell to grow and to divide. An oncogene is a gene whose product stimulates a cell to grow and to divide.
33. The protein called p53 is a tumor suppressor. Mutations of p53 have been found in more than half of all human cancers. Ras is involved in cell division, and mutations in this protein are involved in 30% of human tumors.
34. Viruses have been implicated in many cancers. Retroviruses are particularly dangerous because they insert their DNA into the host’s DNA. When this happens in a tumor-suppressor gene, the tumor suppressor is inactivated, causing cancer. Also, the homology between proto-oncogenes and oncogenes makes it likely that the infection cycle of viruses may be responsible for some proto-oncogenes becoming oncogenic.
35. Virotherapy is the process of using a virus to attempt to treat cancer. There are two strategies for virotherapy. One is to use the virus to attack and kill cancer cells directly. In this case, the virus has a protein on its surface that is specific for a cancer cell. Once inside, it kills the cancer cell. The second is to have the virus ferry a gene into the cancer cell that makes the cell more susceptible to a chemotherapeutic agent.
36. If smoking caused cancer, then everyone who smokes would have cancer, but this is not true. Smoking has been linked to cancer, and it is a strong predictor of future cancer, but cancer is the result of many things going wrong in a cell, and there is no single, definitive cause.
37. A tumor suppressor is a protein that helps control cell growth and division. It is like the brakes on a car, trying to slow down a process. Many cancers are related

to mutation of tumor suppressors. An oncogene produces something that stimulates growth and division. This is like the accelerator of the car. Many other cancers are caused ultimately by overactivation of an oncogene.

38. Ras, Jun, and Fos are all considered oncogenes. In the process of cell division, Ras is a necessary component, but it is usually active only when the cell should be dividing. Oncogenic forms of Ras are overactive and lead to too much cell division. Ras is an early step in the process. Jun and Fos are transcription factors that together make up AP-1, which is involved in the transcription activation pathway involving CBP.
39. Many of the early trials involved specific delivery of an active p53 gene via gene therapy. However, such delivery is impractical for human patients in many cases. Now researchers are looking for drugs that can be taken that will increase the levels of p53.
40. Two drugs, Prima-1 and CP-31398 reactivate mutant p53; nutlins inhibit a protein called MDM2, which is itself a natural inhibitor of p53.
41. p53 can be restored in several ways. One way would be through gene therapy to give the patient functioning copies of the p53 gene if he or she lacks it. Another is to neutralize molecules that naturally inhibit p53. Another is to give the patient drugs that stimulate the production of p53 by stimulating the transcription of the p53 gene. Finally, one could use drugs that would inhibit the transcription of molecules that act as inhibitors of p53.
42. The innate immune system is instrumental in fighting cancer cells. Cell that turn cancerous display specific molecules on their surfaces that act as a help signal. Cells of the innate immune system such as macrophages and natural killer cells attack cells that display these cancer-linked antigens on their surfaces. Often they destroy the cancerous cell, ending the threat. However, if they do not, the presence of the innate immune cell can lead to inflammation. More and more research is showing that inflammation is the switch that takes a precancerous cell and turns it into a full-fledged cancer cell. Thus, innate immune cells that attack a cancer cell but fail to kill it may just make it stronger.
43. The realization that cancer's progression is fueled by inflammation has led to a theory by some scientists that we should spend more time focusing on the symptoms rather than the cure. They believe it is possible that even though potential cancer cells exist, they may not ever grow and spread if we could stop the inflammation.
44. They found more than 30,000 mutations in the melanoma genome and more than 23,000 in lung cancer. This information will make it possible to diagnose cancer much earlier and lead to more effective treatment. For individual patients, it will be possible to see which drugs are likely to be effective in treating the cancer and which ones will not.
45. Most of the mutations associated with melanoma arise from too much exposure to the sun. Likewise, smoking causes most of the DNA errors in lung cancer.
46. Helper T cells
47. The virus binds to the CD4 receptor on the helper T cell via a viral protein called gp120

48. HIV is difficult to kill because it is difficult to find. The reverse transcriptase of HIV is very inaccurate in replication. The result is rapid mutation of HIV. There is also a conformational change of the gp120 protein when it binds to the CD4 receptor on a T cell making it difficult to create antibodies that will mount a useful attack. HIV is also adept at evading the innate immunity system. Lastly, HIV hides from the immune system by cloaking its outer membrane in sugars that are very similar to the natural sugars found on most of its host's cells, rendering the immune system blind to it.
49. The two main approaches are creating vaccines to the virus and using anti-retroviral therapy
50. No, the virus does not kill its host directly. It weakens the immune system via its attack on helper T cells. When the immune system is sufficiently weak, the host dies from opportunistic infections.
51. The common flu is the least lethal, in general, although there have been flu epidemics in the past that were very lethal. SARS is also very lethal. A high proportion of those who got SARS died from it compared to those who were infected by HIV or the flu. HIV is extremely transmissible because it is so slow acting. People may have HIV for decades and not know it, giving them the opportunity to spread it to many more people. SARS was effectively less transmissible because it was so fast acting that the host got sick quickly and was isolated.
52. The gp120 protein on the HIV virus is the molecule that docks with the CD4 receptor on the helper T cell, so it is very important to the action of HIV. The problem is that the gp120 protein changes conformation when it binds, making the attempt to use purified gp120 to make antibodies ineffective. There is also a high mutation rate of the gp120 protein.
53. HAART stands for highly active anti-retroviral therapy. It is based on using a combination of drugs to attack multiple parts of the HIV lifecycle.
54. To be 100% cured, there would have to be zero virus particles in the patient or zero helper T cells that were susceptible to the virus. It always hard to say with certainty that a virus is completely gone, especially with one so good at hiding as HIV. Also, with the high mutation rates of HIV, there is always the small chance that a few virus particles could generate a new form capable of attacking the patients new, presumably immune helper T cells.